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Are higher doses of nicotine replacement more effective for smoking cessation?

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This study determined whether higher dose nicotine patches are more efficacious than lower dose patches among heavy smokers. A randomized double-blind study compared 0, 21, 35, and 42 mg/day of a 24-h patch in 1039 smokers ($\geq$ 30 cigarettes/day) at 12 clinical sites in the USA and one in Australia. Daily patches were used for 6 weeks followed by tapering over the next 10 weeks. Weekly group therapy occurred. Biochemically validated self-reported quit rates at 6, 12, 26, and 52 weeks post-cessation were measured. Quit rates were dose-related at all follow-ups ($p < 0.01$). Continuous, biochemically verified abstinence rates for the 0, 21, 35, and 42 mg doses at the end of treatment (12 weeks) were 16, 24, 30, and 39%. At 6 months, the rates were 13, 20, 20, and 26%. Among the 11 sites with 12 month follow-up ($n = 879$), the quit rates were 7, 13, 9, and 19%. In *post-hoc* tests, none of the active doses were significantly different from each other at any follow-up. The rates of dropouts due to adverse events for 0, 21, 35, and 42 mg were 3, 1, 3, and 6% (p = n.s.). Our results are similar to most prior smaller studies; i.e., in heavy smokers higher doses increase quit rates slightly. Longer durations of treatment may be necessary to show greater advantages from higher doses.

Introduction

Although nicotine replacement doubles quit rates, absolute long-term quit rates in most studies have not exceeded 30% (Foulds, 1993; Hughes, 1993; Law & Tang, 1995; Po, 1993; Silagy, Mant, Fowler, & Lodge, 1994; Tang, Law, & Wald, 1994). This low quit rate may be because nicotine replacement usually provides only 25–75% of the usual nicotine levels from cigarettes (Dale, Hurt, Offord, & Lawson, 1995; Fredrickson *et al.*, Gorsline, Gupta, Dye, & Rolf, 1991) and higher doses might be more effective (Hughes, 1995), especially for heavier smokers.

Clinical trials of whether higher doses of nicotine replacement are more efficacious have produced conflicting results (Hughes, 1995). Results with less dependent smokers have been variable (Hughes, 1995). Among heavier or more dependent smokers, six studies have found that 4 mg nicotine gum produced higher quit rates than 2 mg gum (Garvey, Doherty, Kinnunen, & Vokonas, in press; Glover *et al.*, 1996; Herrera, Franco, Herrera, Partidas, Rolando, & Fagerstrom, 1998; Kornitzer, Kittel, Dramaix, & Bourdoux, 1987; Sachs, 1995; Tonnesen *et al.*, 1988). With nicotine patches, one small inpatient study found 44 mg doses more effective

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(Dale *et al.*, 1995) and three larger more generalizable studies found a large effect (TNSG, 1991), a small effect (Tonnesen *et al.*, 1999) and no effect (Jorenby *et al.*, 1995) of higher doses. In most studies, higher dose patches or gum have not substantially increased side-effects (Dale *et al.*, 1995; Jorenby *et al.*, 1995).

Given the conflicting results for efficacy, we undertook a large, multi-site study of higher doses of a 24-h nicotine patch in a group of heavy smokers. We hypothesized that a larger sample and a wider dose range (0–42 mg) would help clarify whether higher doses were more effective for heavy smokers.

Methods

Subjects

This was a randomized, placebo-controlled trial of the efficacy of 0, 21, 35, and 42 mg doses of 24-h transdermal nicotine systems (Nicoderm, now marketed by SmithKline Beecham Consumer Healthcare) for smoking cessation in heavy smokers. The 12 sites in the USA and one in Australia were outpatient and hospital-based clinics and research laboratories directed by investigators with expertise in treating smoking. These sites recruited smokers by advertisements, referrals, and word of mouth. Major inclusion criteria were that subjects: (a) smoked 30 or more cigarettes/day, (b) were 18–70 years old, (c) had made a prior attempt to stop smoking and were motivated to try again, (d) did not use non-cigarette tobacco, (e) had no past history of cardiac disease or diabetes or current history (in last year) of dermatological diseases, use of psychotropic, steroid or theophylline medications, or alcohol/drug abuse, (f) were using effective birth control and not breast-feeding, and (g) were healthy as determined by medical history, physical exam, vital signs, laboratory tests and EKG. We enrolled 1039 subjects from March to June 1994. All subjects gave written, informed consent.

Subjects were evenly divided between men and women (50% each), were mostly Caucasian (96%) and averaged 43 years of age (SD = 10.2). They averaged 38 cigarettes/day (SD = 9) for 26 years (SD = 10) with an exhaled carbon monoxide of 33 ppm (SD = 12). These subjects were of similar age, sex and race to prior samples of smokers seeking treatment, but due to our inclusion criteria, were heavier smokers and had smoked longer (Hughes, Giovino, Klevens, & Fiore, 1997). On average, our subjects had tried to stop four times (SD = 6), scored eight (SD = 2) on the Fagerstrom Tolerance Questionnaire (Fagerstrom, 1978) and eight (SD = 2) on a 10-point scale of motivation to quit. None of these characteristics differed across the four study groups.

Procedures

Subjects were seen weekly for 6 weeks during initial dosing, biweekly for 10 weeks during a dose taper and then at 6- and 12-month follow-ups. At the pre-cessation visit, subjects were randomly assigned in a double blind manner to 0, 21, 35, or 42 mg/day groups. The expected steady-state nicotine levels for these doses are 0, 10, 17, and 24 ng/ml; which represents approximately 0, 40, 80, and 120% of the mean nicotine level of smokers using 38 cigarettes/day (Fredrickson *et al.*, 1995; Gorsline *et al.*, 1991; Hurt *et al.*, 1993). These patch doses are not commercially available but were delivered by having each subject wear three patches at a time: a 22 cm, a 15 cm and a 7cm patch (Hughes 1993) and varying which of these three patches were active and which were placebo patches.

Subjects applied the three patches on the morning of their quit day and each day thereafter (i.e. 24 h wear) for the next 16 weeks (6 weeks of high dose and 10 weeks of tapering). Patch sites were to be different each day and could be reused after 7 days. If a subject complained of significant insomnia, the investigators could allow bedtime removal of the patch. After the first 6 weeks, subjects receiving active patches were tapered by 7 mg every 2 weeks followed by placebo patches for a total of 10 weeks.

At the pre-cessation visit subjects received a stop-smoking booklet. At this visit and at the first 6 weeks of visits, subjects attended group behavioral therapy for 30–60 min/visit. The groups were composed of 9–15 subjects and were led by counselors, health educators, nurses, physicians or psychologists with experience in counseling smokers. In addition, brief individual counseling (< 10 min) occurred on an *ad-lib* basis during the tapering period visits. Although a standardized treatment manual for the group therapy was not used, guidelines to promote similarity of the content and format of the groups were decided *a priori* at the investigators' meeting.

Measures

At each visit, adverse events, vital signs, expired CO and self-report forms were completed and unused patches collected. Subjects kept a daily diary of patch use, smoking and *DSM-IV* withdrawal symptoms (APA, 1994) for the first 6 weeks. Laboratory tests and an EKG were taken at pre-cessation and then at week 16. The study was terminated by the sponsor prior to the 6- and 12-month follow-up. All sites still collected 6-month data. Eleven of the 13 sites collected 12-month data (879 subjects).

At each visit, subjects who did not attend were counted as smoking. Continuous abstinence was defined using the FDA definition; i.e., self-reported not smoking beginning on day 15 after the quit date and verified by carbon monoxide (CO) ≤ 10 ppm (Jarvis, Tunstall-Pedoe, Feyerabend, Vesey, & Saloojee, 1987) at each visit thereafter. Thus, to be a 1-year continuous abstainer, the smoker would have to attend all sessions, report not smoking after the first 2 weeks and have

negative COs at weeks 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 26, and 52.

Data analysis

The effect of dose on abstinence was tested by a regression model specifically testing the hypothesis that quit rates and side-effects increase with increasing dose. *Post-hoc* testing of individual doses used Duncan's Multiple Range test.

Results

Efficacy

Continuous abstinence increased with increasing dose at the end of the high-dose period (i.e. at 6 weeks, $p < 0.01$), at the end of the taper (12 weeks, $p < 0.005$), at 26-week follow-up ($p < 0.005$) and in the subset followed up at 52 weeks ($p < 0.01$; Table 1). The 42 mg dose appeared to be consistently higher than the 21 mg dose at all follow-ups by + 5–15%; however, none of the active doses was statistically different from one another at any time point. Neither age, sex, cigarettes/day, years of smoking, nor Fagerstrom scores interacted with the effect of dose on outcome.

Safety

The rate of adverse events leading to study termination in the first 4 months was 3, 1, 3, and 6% for the 0, 21, 35 and 42 mg doses (p = n.s.). Eight serious adverse events (0.7%) occurred, three in the placebo group, one in the 21 mg group, one in the 35 mg group and three in the 42 mg group. All subjects recovered without sequelae. Of the five serious adverse events on active doses, one (nausea) was deemed related to nicotine. Adverse events that were dose related ($p < 0.05$) and occurred in at least 5% of those on the 42 mg patch were abnormal dreams (33% of those on 42 mg), nausea (24%), dizziness (16%), headache (14%), any cardiovascular event (8%), asthenia (8%), dyspepsia (8%), myalgia (8%), and vomiting (5%). Cardiovascular events were mostly tachycardia, vasodilation, and palpitation. Subjects who smoked while wearing a patch did not have increased adverse events except for a slight increase in tachycardia (6% of smokers using 42 mg vs. none of the abstainers using 42 mg, p = n.s.).

Table 1. Continuous abstinence rates*

	Dose (mg/day)			
Follow-up (weeks)	0	21	35	44
6	22	51	52	56
16	16	24	30	39
26	13	20	20	26
52†	7	13	9	19

* See text for definition.
† Based on 879 rather than 1039 subjects.

Discussion

Summary of findings

Our major finding is that higher doses of nicotine produce a slight but non-significant increase in the quit rate. This dose effect occurred at all follow-ups; however, none of the higher doses was statistically different from the lower doses. The non-significant increase in abstinence for the 42 mg vs. the 21 mg dose at 12 months was + 6% (13–19%). Six per cent is a small absolute increase in the probability of cessation; however, this translates to a relative increase of + 43% (19%/13%) over that obtained with the standard 21 mg dose. In addition, although a 6% increase is small to a given individual, many have argued that a 6% increase (if real) is a clinically significant increase in a population of smokers (Baillie, Mattick, Hall, & Webster, 1994; Kottke, Battista, DeFriese, & Brekke, 1988).

We also found that higher doses of nicotine appeared safe. Although the incidence of several side-effects increased with dose, the rate of dropouts due to adverse events remained small even with the high dose patch (6% with the 42 mg dose). Only one treatment-related serious adverse event (nausea) occurred at the high dose. Importantly, the rate of adverse events was not greater among those who smoked cigarettes while using higher dose patches vs. those who did not smoke while using the patches. Although these data are encouraging, it is important to remember that all of our subjects smoked ≥ 30 cigarettes/day prior to entering the study. Thus, whether this record of safety would be found in lighter (and perhaps less tolerant) smokers is unknown.

The major assets of our study were that it used a large sample size (n = 1039), a large dose–response range with three active doses, the population most likely to benefit from and be offered higher doses (heavy smokers), and a multi-site design (to mitigate effects idiosyncratic to one site/investigator). In addition, biochemically-confirmed continuous abstinence rates over a 1-year follow-up constituted a rigorous evaluation.

Past studies of the efficacy of higher doses of NRT

Studies of higher doses of nicotine gum differ from those with nicotine patch in that subjects in gum studies were given some freedom to vary dose/day by varying number of pieces/day. Many studies have reported *post-hoc* analyses showing that subjects who used more gums/day (and thus self-selected a higher dose/day) had higher quit rates (Hughes, 1989). However the one study that experimentally varied number of pieces of gum/day found no effect of dose (Gross, Johnson, Sigler, & Stitzer, 1995).

Several trials experimentally tested whether the assigned dose of nicotine gum influenced cessation at 6-week follow-up (when many subjects were still using the gum). At this early follow-up, five trials found a moderate dose-responsivity indicating higher doses of

nicotine gum increased quit rates (Garvey *et al.*, in press; Glover *et al.*, 1996; Herrera *et al.*, 1998; Kornitzer *et al.*, 1987; Tonnesen *et al.*, 1988; and one study did not find this (Tonnesen, Fryd, Hansen, Helsted, Gunnersen, Forchammer, & Stockner, 1988). Five of these six trials also reported a 26-week follow-up when almost all smokers had stopped chewing gum. At this long term follow-up, two studies showed substantial dose-responsivity (Garvey *et al.*, in press; Tonnesen *et al.*, 1988), and three showed slight dose-responsivity (Garvey *et al.*, in press; Glover *et al.*, 1996; Kornitzer *et al.*, 1987; plots of dose-responsivity of all gum studies are available from the first author).

Most prior studies of higher doses of nicotine patch have reported quit rates at 6–8 weeks when most subjects were still using the assigned dose. We calculated our quit rates at this follow-up and have plotted them along with the prior five patch studies (upper panel, Figure 1). In interpreting these data, it is critical to note that studies varied widely in subject selection, amount of behavior therapy, definition of abstinence, etc., and these would be expected to influence both the slope and intercept of the relevant dose–response curves. Nevertheless, visual inspection of the curves can give one an estimate of the extent, if any, of dose-responsivity. At this early follow-up there is evidence of significant dose-responsivity in two trials (Dale *et al.*, 1995; TNSG, 1991), moderate dose-responsivity in the present trial and one other trial (Tonnesen *et al.*, 1999), and little or no dose-responsivity in two trials (Jorenby *et al.*, 1995; Paoletti *et al.*, 1996). When the 6-month data are plotted (lower panel, Figure 1), four of the five prior trials (Dale *et al.*, 1995; Paoletti *et al.*, 1996; TNSG, 1991; Tonnesen *et al.*, 1999) and our trial showed slight dose-responsivity and one (Jorenby *et al.*, 1995) showed no dose responsivity.

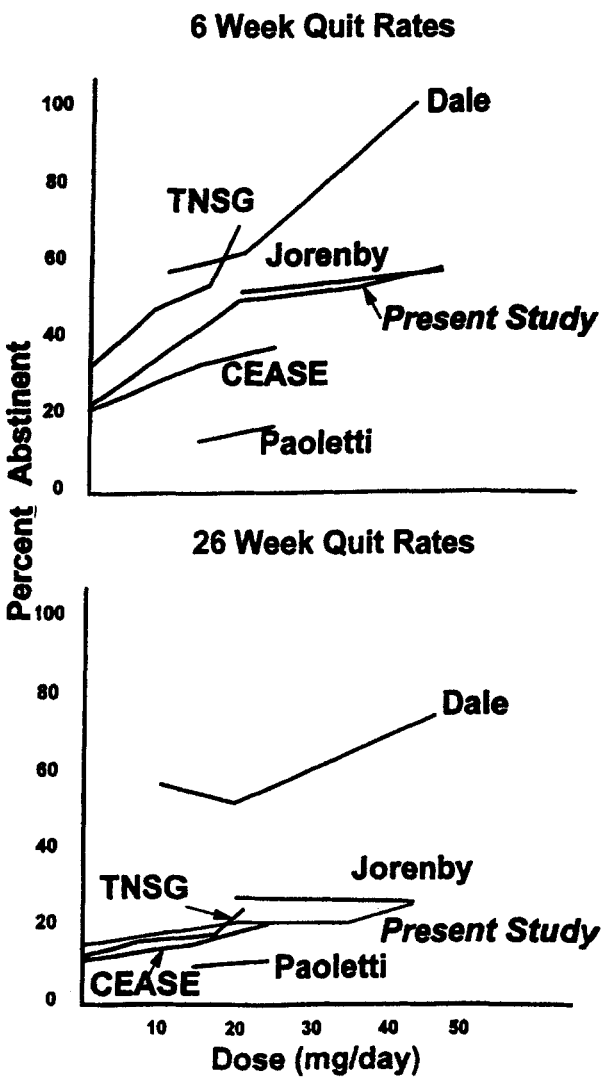

Figure 1. Early (6–8 week) results (upper panel) and long-term (26–52 week) results in prior studies that tested the effect of more than one dose of transdermal nicotine on smoking abstinence.

Another set of studies tested dose-responsivity of patches in a different manner. These studies tested the hypothesis that smokers who obtain a higher percentage replacement of nicotine from patches have higher quit rates than those who obtain a lower percentage replacement (Dale *et al.*, 1995; Fredrickson *et al.*, 1995; Kozak, Fagerstrom, & Sawe, 1995; Sachs, Benowitz, & Bostrom, 1995). Most, but not all, of these studies suggest greater replacement improves quit rates (Dale *et al.*, 1995; Fredrickson *et al.*, 1995; Kozak *et al.*, 1995; Sachs *et al.*, 1995), however, there are methodological problems interpreting such studies (Hughes, 1995).

If this percentage replacement hypothesis is true, then in the present data set, we should expect to see an interaction between cigarettes/day and treatment assignment such that lower rate smokers would especially benefit from higher doses. We did not find this; however, our sample was fairly homogenous due to our inclusion criteria of >30 cigarettes/day and we did not measure cotinine levels nor stratify *a priori* according to nicotine or cotinine levels; thus, our study may have been an inadequate test of the replacement hypothesis.

A final set of studies indirectly tested the dose-responsivity of nicotine replacement by comparing combined nicotine gum + patch vs. either treatment alone (Fagerstrom, 1994). Such studies do indicate combined treatment is more effective. Although this may be due to increased doses being delivered it may also be due to increased flexibility of dosing (gum + patch vs. patch; Kornitzer, Boutsen, Dramaix, Thijs, & Gustavsson, 1995) or better compliance (gum + patch vs. gum; Puska, Korhonen, Vartiaaninen, Urjanheimo, Gustavsson, & Westin, 1995).

In summary, our results and those of the other clinical trials (Figures 1 and 2) clearly suggest a dose–response effect for nicotine replacement on abstinence; however, the therapeutic dose–response curve for nicotine is shallow. Interestingly, this flat dose–response pattern is seen in both humans and non-humans (Henningfield & Woodson, 1989) when endpoints of self-administration (Valentine, Hokanson, Matta, & Sharp, 1997), heart rate acceleration (Benowitz & Gourlay, 1997), withdrawal relief (Hughes, Gust, Keenan, & Fenwick, 1990; Jorenby *et al.*, 1995; TNSG, 1991), and other measures are taken. This replicability across species and outcomes suggests validity for this conclusion.

On the other hand, the flat dose-responsivity for abstinence could be due to a methodological issue, i.e., the short duration of the high dose treatment. In most of the studies including ours, the duration of high nicotine dose therapy was 6 weeks or less. A comparison of the upper and lower portions of Figure 1 suggests dose influences outcome more at early follow-up than at later follow-up. However, the CEASE trial did test higher doses (25 mg/16 h) for a longer period and did not find dose effects greater with longer follow-up (Tonnesen *et al.*, 1999).

Past studies of adverse events

One important factor in deciding whether higher doses of nicotine should be used is the side-effect profile of higher doses. The present study found few clinically significant adverse effects at high doses. Among the patch studies cited above, the only one to report dropouts due to adverse events reported results similar to ours, i.e., dropouts increased somewhat with increasing dose but were low overall (<5%; Jorenby *et al.*, 1995). We found eight significant events (0.7%) but all subjects recovered and only one was deemed treatment-related. One prior small study of high doses (44 mg) did not report any clinically significant adverse events (Dale *et al.*, 1995). A large study of high-doses found that four of the 252 subjects (2%) receiving 44-mg patches had significant events. Three of these subjects recovered from these events and one had a residual problem.

In terms of individual adverse events, both one prior study (Jorenby *et al.*, 1995) and ours found higher rates of nausea or vomiting with higher doses with incidence rates of 28 and 24% in the 42-mg groups. One study reported more sleep disturbances (Jorenby *et al.*, 1995) and another higher skin reactions (Fredrickson *et al.*, 1995) with higher doses. We did not find higher incidence of abnormal dreams, perhaps because we allowed subjects to remove patches if they had sleep problems. We did not find a higher incidence of skin reactions, perhaps because we used three patches to deliver the nicotine.

Many subjects in the present trial and in the prior trials smoked while using the high-dose patch. There was no indication that subjects who did so were at a higher risk of cardiac or other adverse events (Dale *et al.*, 1995; Fredrickson *et al.*, 1995; Jorenby *et al.*, 1995. Thus, our data and that from the prior high dose studies are consistent with other epidemiological and experimental data that indicate the prior concerns about smoking while wearing a patch have been overstated (Benowitz & Gourlay, 1997).

Conclusions

Although we demonstrated a dose–response relationship between nicotine and cessation outcome, quit rates were only 6% higher with higher doses of nicotine than standard doses and this difference was not statistically significant. Thus, one interpretation of our results is that higher doses are not clinically indicated. A different interpretation is that smoking cessation is so important, and the risk of higher doses is so small, that it is worthwhile to use higher doses to capture this possible additional 6%.

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